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A great disturbance in the force: IL-2 receptor defects disrupt immune homeostasis

Joseph D. Hernandez, MD PhD[1], **Elena W.Y. Hsieh, MD**[2,3]

[1]Department of Pediatrics, Division of Allergy, Immunology and Rheumatology, School of Medicine, Stanford University, Lucile Packard Children's Hospital

[2]Department of Pediatrics, Section of Allergy and Immunology, School of Medicine, University of Colorado, Children's Hospital Colorado

[3]Department of Immunology and Microbiology, School of Medicine, University of Colorado

Abstract

Purpose of review—This review highlights how inborn errors of immunity (IEI) due to interleukin-2 receptor (IL-2R) subunit defects may result in children presenting with a wide variety of infectious and inflammatory presentations beyond typical X-linked severe combined immune deficiency (X-SCID) associated with IL-2Rγ.

Recent Findings—Newborn screening (NBS) has made diagnosis of typical SCID presenting with severe infections less common. Instead, infants are typically diagnosed in the first days of life when they appear healthy. Although earlier diagnosis has improved clinical outcomes for X-SCID, atypical SCID or other IEI not detected on NBS may present with more limited infectious presentations and/or profound immune dysregulation. Early management to prevent/control infections and reduce inflammatory complications is important for optimal outcomes of definitive therapies. Hematopoietic stem cell transplant (HSCT) is curative for IL-2Rα, IL-2Rβ, and IL-2Rγ defects, but gene therapy may yield comparable results for X-SCID.

Summary—Defects in IL-2R subunits present with infectious and inflammatory phenotypes that should raise clinician's concern for IEI. Immunophenotyping may support the suspicion for diagnosis, but ultimately genetic studies will confirm the diagnosis and enable family counseling. Management of infectious and inflammatory complications will determine the success of gene therapy or HSCT.

Keywords

Severe combined immunodeficiency (SCID); IL-2R; inborn errors of immunity (IEI); cytomegalovirus (CMV); immune dysregulation

CORRESPONDING AUTHOR: Elena W.Y. Hsieh MD, Associate Professor, Department of Pediatrics, Section of Allergy and Immunology, Department of Immunology and Microbiology, 12800 East 19th Avenue, Mail Stop 8333, Room P18-8117, Aurora, CO 80045, Ph: 303-724-9650, elena.hsieh@cuanschutz.edu.

AUTHOR CONTRIBUTIONS

JDH and EWYH wrote the manuscript and conceptualized this review.

CONFLICT OF INTEREST

There are no conflicts of interest.

INTRODUCTION

Over the last 50 years interleukin-2 (IL-2) has emerged as the quintessential immunoregulatory cytokine with dual roles in both promotion of host defense and immune tolerance. Human defects in IL-2 receptor subunits (IL-2Rs) have confirmed the roles of IL-2 and related cytokines in host defense against a variety of pathogens, as defects in these subunits can lead to profound immune deficiency or more selective defects in anti-microbial response (Figure 1). Defects in IL-2Rs can also present with severe immune dysregulation and autoimmunity. In this review, we will discuss how inborn errors of immunity (IEI) in the various IL-2Rs may present clinically with either a profound and global immune deficiency, or a more limited immune deficiency with immune dysregulation, with a focus on diagnosis and treatment strategies.

IL-2 receptor structure and expression in the immune system

The high-affinity IL-2R consists of three polypeptide chains: alpha (IL-2Rα, CD25), beta (IL-2Rβ, CD122), and gamma (IL-2Rγ, γ_c, CD132) (1, 2) (Figure 2). IL-2Rβ and IL-2Rγ are required for downstream signal transduction by IL-2, and when expressed in the absence of IL-2Rα form the intermediate-affinity IL-2R which binds to IL-2 with ~100 fold lower affinity than the high affinity trimeric receptor (3, 4). The various subunits are expressed in a wide variety of cell types in the immune system, and some serve as subunits for other cytokine receptors (Figure 2).

IL-2Rα only binds to IL-2 and does not serve as a subunit for other cytokine receptors (Figure 2A). IL-2Rα is not expressed on resting T cells but is upregulated on activated/effector conventional T cells and constitutively expressed on regulatory T cells (Tregs), increasing their ability to bind and respond to IL-2 (5, 6) (Figure 2B). Although not required for Treg development, IL-2Rα expression is essential for Treg function (7, 8). IL-2Rα is also expressed on immature $CD56^{bright}$ NK cells that proliferate and produce cytokines when stimulated with IL-2 (9) (Figure 2B).

IL-2Rβ is a shared component of both the IL-2R and the IL-15R (Figure 2A). Naïve T cells express IL-2Rβ at low levels and cells are minimally responsive to IL-2 (Figure 2B). However, IL-2Rβ is upregulated on effector and memory T cell populations (6). IL-15 regulates CD8 memory T cell and NK cell survival, proliferation, and effector functions indicating a critical role in protective immunity to viral infections (Figure 2) (10, 11).

IL-2Rγ is a shared component of multiple cytokine receptors (IL-2, 4, 7, 9, 15, and 21) and is critical for signal transduction for each of these cytokines (12) (Figure 2A). Developing, naïve, effector, and memory T cells require IL-2Rγ for survival, differentiation, and effector functions (6, 12, 13) (Figure 2B). IL-15 signaling through IL-2Rβγ is required for NK cell development and survival (14). In contrast, B cells are not dependent on IL-2Rγ for early development (in humans), but IL-4 and IL-21 signaling through IL-2Rγ is necessary for differentiation into antibody secreting plasmablasts and class switching (15, 16).

IMMUNODEFICIENCY IN CLASSICAL IL-2Rγ NULL DEFECTS: “BOY IN THE BUBBLE”

IL-2Rγ deficiencies were the first human defects in IL-2 signaling described, resulting in a $T^{-}B^{+}NK^{-}$ severe combined immune deficiency (SCID), manifesting as a profound and global immune deficiency (17) (Figure 1). Its X-linked inheritance pattern led to the moniker of X-SCID and “boy in the bubble.” X-SCID is the most common cause of SCID in the US and Europe (18–20). Most patients with IL-2Rγ deficiency present with profound T and NK cell deficiencies while B cell function is decreased but cell numbers are largely intact (15, 16). However, some patients have variable numbers of T, B and NK cells. In some cases, this may be explained by partial IL-2Rγ function or maternal engraftment of T cells, but in many other cases there is no clear explanation for variable cell numbers (21). Indeed, even siblings with identical genetic mutations may present with divergent immune phenotypes (21).

Clinical presentation of X-linked SCID: From sick kids to Guthrie cards—The widespread immune defects resulting from X-SCID result in patients presenting with diverse types of infections from i) unusual/atypical organisms, or ii) common organisms with recurrent and/or severe presentations. These infections, along with a family history of primary immune deficiency and failure to thrive, form the basis of the “10 warning signs of primary immune deficiency,” which are widely used but have limited sensitivity and specificity in the identification of patients with IEI (22, 23).

Some opportunistic infections are more suggestive of SCID because host defense against these infections require functional T cell immunity. *Pneumocystis jirovecii* (PJP) is an early presenting infection in patients with X-SCID, as CD4 T cells coordinate inflammatory responses and recruitment of effector cells necessary for clearance (24, 25). IL-17 immunity, driven largely by Th_{17} CD4 T cells, but also to a lesser extent by innate lymphoid cells and NKT cells, is critical for host defense against fungal infections through recruitment of neutrophils, particularly at mucosal surfaces. Mucocutaneous candidiasis is a common presentation of SCID, and several cases of invasive candidiasis (pneumonia or meningitis) have also been described (26). Control of herpesvirus infections, particularly cytomegalovirus (CMV) and Epstein Barr virus (EBV), is dependent on T cell and NK cell activity, and therefore EBV and CMV viremia, enteritis, pneumonitis, and meningitis are major causes of morbidity and mortality in X-SCID patients (27).

SCID patients may also present with severe manifestations of more ordinary pediatric infections. Normally mundane respiratory viruses that are easily contracted in community or family settings, such as paramyxovirus and adenovirus, are life threatening in X-SCID patients (28, 29). With waning maternal immunoglobulins, SCID patients can present with recurrent or invasive bacterial infections such as otitis, bacteremia, or meningitis (21).

SCID diagnosis was targeted for newborn screening (NBS) given i) the high morbidity and mortality rate in early infancy due to infections, ii) the negative impact of pre-existing infections and resulting organ damage on survival post-transplant, and iii) the improved survival and outcome of early hematopoietic stem cell transplant (HSCT) in infants identified due to family history (20, 30, 31). T cell receptor (TCR) excision circles (TRECs) are stable circular DNA molecules produced as a byproduct of TCR rearrangement; TRECs can be quantitated from a blood spot using polymerase chain reaction (PCR) to indicate the

presence of T cells (18). NBS for SCID using TREC assays started pilot studies in 2008, and by 2019 it was adopted by all US states and multiple countries around the world (18). Rates of SCID diagnoses due to infection and/or family history steadily declined from ~90% cases to 10% cases by 2016, resulting in reduced pre-transplant infections and survival comparable to early diagnosis based on family history (19).

Despite the improvements realized by NBS, several challenges remain. Over 40% of infants still develop infections prior to transplant, with respiratory virus and CMV infections being the most common (19, 29). CMV can be shed intermittently in breast milk, therefore CMV transmission can occur in the brief interval between collection of NBS cards and confirmation of diagnosis, resulting in devastating consequences for infants with SCID (18, 29). There is also a risk of disseminated disease from BCG vaccination that is given in the nursery (32). Furthermore, patients with atypical SCID (and non-SCID IEI) will be missed by NBS due to the incomplete absence of T cells (18, 33), resulting in later diagnosis, increased complications, and higher likelihood of poor outcomes.

Treatment of X-linked SCID: Life beyond the bubble—HSCT has been the treatment of choice since the first successful transplant was reported for X-SCID in 1968 (34). Pre-transplant care remains variable (29), but typically includes infection prophylaxis with immunoglobulin replacement and trimethoprim-sulfamethoxazole for PJP. Many centers also prophylax with acyclovir/ganciclovir for CMV, fluconazole for fungal infections, and azithromycin for atypical mycobacteria. Given the high rates of CMV even with diagnosis by NBS, there is growing consensus that breast feeding should be stopped at first concern for SCID (29). Although many infants remain hospitalized while awaiting HSCT, some centers may consider home stays for infants prior to transplant dependent on household exposures (29).

Consortiums have been formed to collect clinical data on these rare transplants, with the goal of identifying factors and designing protocols that may lead to improved outcomes. At US centers, HSCT at less that 3.5 months of age was associated with the highest overall survival rates (30, 31), while the European registry did not find that age at HSCT is associated with overall survival (20). Multiple studies have identified infection prior to transplant, and particularly active infection at HSCT, as being associated with survival rates up to 40% lower than uninfected children (19, 20, 30, 35). Matched related transplants were associated with the best survival in most studies, while HLA mismatched transplants were associated with worse outcomes (30, 35). Mismatched and even haplo-identical transplants can be performed with lower rates of graft-versus-host disease (GVHD) graft rejection, and survival if the graft is TCRαβ and/or CD19 depleted (31, 36, 37).

Over the last decade, conditioning regimens have become an increasingly recognized factor in determining long term immune reconstitution. Myeloablative conditioning or reduced intensity conditioning resulted in higher T cell counts (19, 30) and independence from immunoglobulin (20, 30, 36). Poor B cell reconstitution with lack of memory B cells and persistent humoral dysfunction may be particularly problematic in patients with X-SCID transplanted without conditioning as recipient B cells are unable to to respond to IL-21, class switch or differentiate to plasmablasts (15, 16, 38) (Figure 2). A lack of early

immune reconstitution as measured by low CD3+ T cell count, low naïve CD4+ naïve T cell numbers, or poor TCR diversity predicted a need for repeat transplant or risk of death (19, 20, 39), whereas, naïve CD4+ T cell count >100 predicted independence from immunoglobulin (20).

Although HSCT survival and immune reconstitution have improved over the last decades, there may be times that a suitable (matched) donor is unavailable, and even with a good HLA match GVHD remains a potential complication associated with decreased survival (19, 20, 30). Because of these ongoing concerns, X-SCID was one of the first diseases targeted for gene. Expression of IL-2Rγ in even a small number of cells may be sufficient to reconstitute the T cell compartment as it results in a survival and proliferative advantage that was previously observed in patients with spontaneous reversions (40–42). The first successful trials of gene therapy expressed *IL2RG* under the control of endogenous transcriptional elements in the long terminal repeat of the retroviral vector (43, 44). Although these patients had good overall survival and T cell reconstitution many of the patients required long term immunoglobulin replacement (45, 46). More worrisome however, was the development of T cell acute lymphoblastic leukemia in 30% of the patients due to transcriptional activation of proto-oncogenes by the vector through non-random integration, resulting in one patient's death (47–50). Following efforts to develop safer "self-inactivating" retroviral and lentiviral vectors, X-SCID patients were treated without any reports of leukemogenesis; all achieved good T cell reconstitution but only a minority of patients achieved independence from immunoglobulin and/or had adequate vaccine responses despite evidence of B cell transduction (51–53).

Only one single center, retrospective study has directly compared haploidentical HSCT to gene therapy outcomes (42, 54). Patients treated with gene therapy demonstrated increased T cell reconstitution and function, however HSCT patients received anti-thymoglobulin (ATG) that may have delayed T cell reconstitution. Better comparisons between HSCT and gene therapy are needed. Future studies will continue to explore the effects of conditioning on immune reconstitution, including novel conditioning regimens with non-toxic monoclonal antibodies and the use of gene-editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) (42).

IMMUNE DYSREGULATION IN IL-2R SUBUNIT DEFECTS: "IPEX-LIKE" DISORDERS

While absent IL-2Rγ function leads to severe immune deficiency, defects in IL-2Rα, IL-2Rβ, and some hypomorphic mutations in IL-2Rγ result in combined immune deficiency with immune dysregulation (55–58). Patients with IL-2Rα defects have decreased responsiveness to IL-2 but are still able to signal through the intermediate affinity receptor; and other cytokine signaling remains intact. Patients with absent expression or functional null IL-2Rβ defects cannot respond to IL-2/15; patients with hypomorphic variants exhibit dysregulated IL-2/15 signal transduction with increased baseline IL-2/15R engagement due to increased circulating serum IL-2/15 cytokines and hyporesponsiveness to *ex vivo* IL-2/15 stimulation (59, 60). Some *IL2RG* mutations (including p.Arg222Ser) (33, 61) may differentially affect cytokine signaling with signaling transduction least affected for IL-4 and most affected for IL-21 (IL-4<IL-2/IL-15<IL-7<IL-21).

Defects in IL-2Rα and IL-2Rβ result in defective IL-2 downstream signaling, thereby resulting in decreased host defense functions, but also a loss of tolerance through decreased Treg numbers and function (Figure 1). Patients with IL-2Rα defects have decreased or normal Treg numbers, but they are non-functional (8, 62–64), while patients with IL-2Rβ defect have drastically reduced Treg numbers (59, 60). Patients with these mutations have variable clinical presentations with a mix of inflammatory and infectious manifestations.

Clinical presentation of CD25 deficiency, IL-2Rβ defects, and hypomorphic IL-2Rγ defects: From the "bubble boy" to IPEX-like disorders—Patients with IL-2Rα, IL-2Rβ, and a small subset of IL-2Rγ defects present with an IPEX-like syndrome. They present with lymphoproliferation (lymphadenopathy and hepatosplenomegaly with lymphocytic infiltration of tissues) with various tissue specific inflammation and autoimmune disease including: dermatitis, vasculitis, diarrhea/enteritis, insulin dependent diabetes, thyroiditis, and autoimmune blood dyscrasias (8, 55–57, 59, 60, 62, 64–68). Immune dysregulation and autoimmunity are more common in SCID patients with atypical presentations that include greater numbers of lymphocytes and typically occurs in the first few months of life (19, 21).

These patients may also present with a variety of bacterial, viral, and fungal infections. Although these may include some classic opportunistic infections such as candidiasis, no IL-2Rα or IL-2Rβ, deficiencies presented with PJP pneumonia, and IL-2Rγ patients with atypical phenotypes presented with PJP less frequently than patients with typical X-SCID (21, 55). IL-2Rα, IL-2Rβ, and atypical IL-2Rγ patients presented with prominent viral infections, including severe respiratory viral infections, but most notably CMV and other herpesvirus infections (21, 55, 69). Strikingly, all of the IL-2Rα or IL-2Rβ patients that survived the neonatal period developed herpesvirus infections, with 5/7 IL-2Rβ and 5/5 IL-2Rβ patients developing CMV disease (8, 55, 59, 60, 62, 64–68).

The immune phenotype of these patients is quite variable (Table 1). IL-2Rα and IL-2Rβ deficiency may present with normal, decreased, or even increased numbers of T cells and other lymphocytes. T cell subset analysis demonstrated abnormal CD4:CD8 ratios and increased numbers of activated or memory CD4+CD45RO+ cells (8, 55, 59, 60, 63, 67). Atypical IL-2Rγ patients present with modestly reduced to normal T cell numbers and variable NK cell numbers (21, 56, 58). Consistent with chronic inflammation, many of IL-2Rα and IL-2Rβ deficient patients presented with elevated IgG with variable vaccine responses (8, 59, 60, 63, 64, 66–68). Some patients with atypical X-SCID may also present with dysgammaglobulinemia and elevated IgG (69).

Patients with atypical X-SCID, IL-2Rα, or IL-2Rβ patients have significant numbers of T cells and are therefore unlikely to be detected via NBS (18, 21, 33, 70). A high index of suspicion based on clinical findings is required to make the diagnosis. Immunological phenotypes that would indicate a defect in IL-2Rβ signaling, can be assessed at various reference labs (Table 1). First, these patients demonstrate increased levels of plasma IL-2 (8, 59, 60). Second, CD8 T cells in IL-2Rβ deficient patients express low or no CD57, a marker of T cell exhaustion or senescence in chronic viral infections and cancers (71) (data not published). In patients with hypomorphic IL-2Rβ defects or CD25 deficiency,

a larger proportion of NK cells demonstrate a less mature CD56^{bright} phenotype (59, 60, 72) (Table 1). This is in contrast with IL-2Rβ expression or functional null patients where there is a lack of NK cells, akin the *Il2rb*$^{-/-}$ mice. This same phenomenon of CD56^{bright} NK cell expansion has also been observed in multiple sclerosis patients undergoing CD25 depletion via alemtuzumab; but not in IEI patients with signal transducers and activators of transcription (STAT)5b deficiency, reflecting the complexity of the IL-2/STAT5 axis in human NK cell development (73). Definitive diagnosis requires genetic testing.

Treatment of IL-2R defects with immune dysregulation: Righting the ship in a cytokine storm—Although less problematic than for the X-SCID patients, IL-2Rα, IL-2Rβ, and atypical IL-2Rγ deficiency patients require infectious prophylaxis. As CMV and other herpes virus infections were the most problematic infections for these patients, they should receive (val)ganciclovir prophylaxis and be monitored regularly for CMV infection (8, 59, 60, 66, 68). A couple of CD25 deficient patients also received antifungal prophylaxis, which is likely warranted given multiple IL-2Rα and β patients suffered from candidiasis (8, 55, 59, 63, 67, 68). Although several CD25 deficiency patients were also treated with prophylactic antibiotics, including for PJP, it is unclear if this is necessary given none of the patients were reported to have PJP infections. Immunoglobulin replacement was given to a couple patients but is unlikely to be necessary in all cases given most patients have elevated IgG levels and some have normal vaccine responses (55, 63, 66).

Given that inflammation and autoimmunity are the prominent clinical complications for patients with *IL2RA*, *IL2RB*, and a small subset of *IL2RG* mutations, immunosuppression must be used. The majority of cases used steroids with some improvement in inflammation, lymphoproliferation, and autoimmunity (8, 59, 60, 64, 66, 67). A wide variety of steroid-sparing agents were used with mixed benefit. Four of the CD25 and IL-2Rβ deficient patients were treated with sirolimus to good effect, which. Sirolimus has been used successfully in other IEIs where lymphoproliferation and autoimmunity are prominent features and may have the added benefit of preserving Treg function (8, 59, 60, 64, 74–76). Although many of these patients were treated prior to the availability of our current abundance of biologic agents, one IL-2Rα and one IL-2Rβ patient received rituximab (60, 66) and one IL-2Rβ patient received infliximab (60) with clinical benefit.

An emerging therapeutic target for patients with IEIs resulting in lymphoproliferation and autoimmunity are the Janus Kinases (JAK) themselves. Small molecule inhibitors of JAKs (JAKinib) are approved to treat autoimmune, inflammatory, and hematologic conditions; but have also been successfully used to treat STAT1 and STAT3 gain-of-function and interferonopathies (77–79). Theoretically JAKinib could be used to treat any disease with increased JAK/STAT signaling (Figure 2). In some patients with STAT1 gain-of-function, dramatic improvement in autoimmune manifestations were observed, but the overall experience has been mixed (77, 78). The first-generation inhibitors have significant side effects including: infections, reactivation of viruses, bone marrow suppression, thromboembolism, and a withdrawal syndrome; side-effects may be reduced with newer-generation JAKinib that are more target specific (79). Although disease specific dosing has yet to be established for IEIs, especially in children, pediatric dosing for other indications has been established.

Similar to patients with X-SCID, patients with IL-2Rα or IL-2Rβ deficiencies and atypical X-SCID will ultimately require HSCT. Because these patients suffer from immune dysregulation, they will likely require higher levels of donor chimerism; therefore, particular attention needs to be paid to pre-transplant conditioning and donor selection. Furthermore, control of hyperinflammation prior to transplant may reduce the risk of GVHD and graft failure (80, 81). Transplant of three IL-2Rα deficient patients following myeloablative/cytoreductive conditioning resulted in resolution of symptoms (62, 63, 67). HSCT of five IL-2Rβ deficient patients have been reported, one patient died from multiorgan failure following graft failure and persistent inflammation and one patient died from respiratory failure, presumably from CMV (59, 60, 68). Transplantation of atypical X-SCID patients requires cytoreductive conditioning (27, 33, 56, 69), in one case the transplant had to be repeated after initial transplant without conditioning resulted in graft failure.

Gene therapy for IL-2Rγ deficiency has been performed as described above. In patients with atypical cases of X-SCID there may a diminished selective advantage to transformed cells reducing T cell recovery (42). Gene therapy has not been used for IL-2Rα and IL-2Rβ deficiencies, but presumably these patients would also be more difficult to treat with gene therapy as they will not have the same selective advantage as the X-SCID patients, and the resolution of the inflammation/autoimmunity would likely depend on high levels of transformed T cells after gene therapy. In addition, a recent case report raises the possibility that increased levels of IL2-Rα expression may result in inflammation/autoimmunity, specifically inflammatory bowel disease (IBD), implying that gene therapy for *IL2RA* would need to achieve native levels of expression (82).

CONCLUSION

NBS has made early diagnosis of typical SCID the norm. However, many IEI, including other defects in IL-2Rs will not be detected on NBS, necessitating that clinicians maintain a high degree of suspicion for patients presenting with unusual infectious or inflammatory/autoimmune histories. Management of infections and inflammatory/autoimmune complications in these patients will determine how they fare when they undergo HSCT or gene therapy. Further outcomes data will be useful in deciding on optimal treatments for these patients.

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REFERENCES

1. Kim HP, Imbert J, Leonard WJ. Both integrated and differential regulation of components of the IL-2/IL-2 receptor system. Cytokine Growth Factor Rev. 2006;17(5):349–66. [PubMed: 16911870]
2. Wang X, Rickert M, Garcia KC. Structure of the quaternary complex of interleukin-2 with its alpha, beta, and gammac receptors. Science. 2005;310(5751):1159–63. [PubMed: 16293754]

3. Nakamura Y, Russell SM, Mess SA, et al. Heterodimerization of the IL-2 receptor beta- and gamma-chain cytoplasmic domains is required for signalling. Nature. 1994;369(6478):330–3. [PubMed: 8183373]
4. Nelson BH, Lord JD, Greenberg PD. Cytoplasmic domains of the interleukin-2 receptor beta and gamma chains mediate the signal for T-cell proliferation. Nature. 1994;369(6478):333–6. [PubMed: 7514277]
5. Ross SH, Cantrell DA. Signaling and Function of Interleukin-2 in T Lymphocytes. Annu Rev Immunol. 2018;36:411–33. [PubMed: 29677473]
6. Rochman Y, Spolski R, Leonard WJ. New insights into the regulation of T cells by gamma(c) family cytokines. Nat Rev Immunol. 2009;9(7):480–90. [PubMed: 19543225]
7. Furtado GC, Curotto de Lafaille MA, Kutchukhidze N, et al. Interleukin 2 signaling is required for CD4(+) regulatory T cell function. J Exp Med. 2002;196(6):851–7. [PubMed: 12235217]
8. Goudy K, Aydin D, Barzaghi F, et al. Human IL2RA null mutation mediates immunodeficiency with lymphoproliferation and autoimmunity. Clin Immunol. 2013;146(3):248–61. [PubMed: 23416241]
9. Carson WE, Giri JG, Lindemann MJ, et al. Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. J Exp Med. 1994;180(4):1395–403. [PubMed: 7523571]
10. Nolz JC, Richer MJ. Control of memory CD8(+) T cell longevity and effector functions by IL-15. Mol Immunol. 2020;117:180–8. [PubMed: 31816491]
11. Abel AM, Yang C, Thakar MS, et al. Natural Killer Cells: Development, Maturation, and Clinical Utilization. Front Immunol. 2018;9:1869. [PubMed: 30150991]
12. Liao W, Lin JX, Leonard WJ. Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. Immunity. 2013;38(1):13–25. [PubMed: 23352221]
13. Chen D, Tang TX, Deng H, et al. Interleukin-7 Biology and Its Effects on Immune Cells: Mediator of Generation, Differentiation, Survival, and Homeostasis. Front Immunol. 2021;12:747324. [PubMed: 34925323]
14. Cao X, Shores EW, Hu-Li J, et al. Defective lymphoid development in mice lacking expression of the common cytokine receptor gamma chain. Immunity. 1995;2(3):223–38. [PubMed: 7697543]
15. Buckley RH, Win CM, Moser BK, et al. Post-transplantation B cell function in different molecular types of SCID. J Clin Immunol. 2013;33(1):96–110. [PubMed: 23001410]
16. Recher M, Berglund LJ, Avery DT, et al. IL-21 is the primary common gamma chain-binding cytokine required for human B-cell differentiation in vivo. Blood. 2011;118(26):6824–35. [PubMed: 22039266]
17. Noguchi M, Yi H, Rosenblatt HM, et al. Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. Cell. 1993;73(1):147–57. [PubMed: 8462096]
18. Currier R, Puck JM. SCID newborn screening: What we've learned. J Allergy Clin Immunol. 2021;147(2):417–26. [PubMed: 33551023]
19. Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017;130(25):2718–27. [PubMed: 29021228]
20. Lankester AC, Neven B, Mahlaoui N, et al. Hematopoietic cell transplantation in severe combined immunodeficiency: The SCETIDE 2006–2014 European cohort. J Allergy Clin Immunol. 2022;149(5):1744–54 e8. [PubMed: 34718043] Highlights factors influencing survival and outcomes following HSCT in Europe and how they differ from US experience
21. Cirillo E, Cancrini C, Azzari C, et al. Clinical, Immunological, and Molecular Features of Typical and Atypical Severe Combined Immunodeficiency: Report of the Italian Primary Immunodeficiency Network. Front Immunol. 2019;10:1908. [PubMed: 31456805]
22. Lankisch P, Schiffner J, Ghosh S, et al. The Duesseldorf warning signs for primary immunodeficiency: is it time to change the rules? J Clin Immunol. 2015;35(3):273–9. [PubMed: 25749910]
23. Subbarayan A, Colarusso G, Hughes SM, et al. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics. 2011;127(5):810–6. [PubMed: 21482601]

24. Kolls JK, Habetz S, Shean MK, et al. IFN-gamma and CD8+ T cells restore host defenses against Pneumocystis carinii in mice depleted of CD4+ T cells. J Immunol. 1999;162(5):2890–4. [PubMed: 10072538]
25. Lionakis MS. Primary immunodeficiencies and invasive fungal infection: when to suspect and how to diagnose and manage. Curr Opin Infect Dis. 2019;32(6):531–7. [PubMed: 31567735]
26. Antachopoulos C, Walsh TJ, Roilides E. Fungal infections in primary immunodeficiencies. Eur J Pediatr. 2007;166(11):1099–117. [PubMed: 17551753]
27. Dorsey MJ, Dvorak CC, Cowan MJ, et al. Treatment of infants identified as having severe combined immunodeficiency by means of newborn screening. J Allergy Clin Immunol. 2017;139(3):733–42. [PubMed: 28270365]
28. Crooks BN, Taylor CE, Turner AJ, et al. Respiratory viral infections in primary immune deficiencies: significance and relevance to clinical outcome in a single BMT unit. Bone Marrow Transplant. 2000;26(10):1097–102. [PubMed: 11108309]
29. Dorsey MJ, Wright NAM, Chaimowitz NS, et al. Infections in Infants with SCID: Isolation, Infection Screening, and Prophylaxis in PIDTC Centers. J Clin Immunol. 2021;41(1):38–50. [PubMed: 33006109] ** Demonstrates how infectious presentations in SCID have changed since NBS, including persistent problems with CMV and EBV. A survey of transplant centers demonstrated significant differences in pre-transplant care
30. Pai SY, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000–2009. N Engl J Med. 2014;371(5):434–46. [PubMed: 25075835]
31. Hardin O, Lokhnygina Y, Buckley RH. Long-Term Clinical Outcomes of Severe Combined Immunodeficiency Patients Given Nonablative Marrow Transplants. J Allergy Clin Immunol Pract. 2022;10(4):1077–83. [PubMed: 34942385] *Infants treated with non-conditioned T cell depleted transplants at the largest single transplant center are generally healthy but require long-term immunoglobulin
32. Cocchi N, Jacobsen EM, Hoenig M, et al. BCG Disease in SCID: Three Decades of Experience in a Pediatric Transplant Center. J Clin Immunol. 2022;42(1):195–8. [PubMed: 34622389]
33. Kitcharoensakkul M, Aluri J, Elsharkawi I, et al. A Case of Severe Combined Immunodeficiency Missed by Newborn Screening. J Clin Immunol. 2021;41(6):1352–5. [PubMed: 33712943]
34. Gatti RA, Meuwissen HJ, Allen HD, et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet. 1968;2(7583):1366–9. [PubMed: 4177932]
35. Miyamoto S, Umeda K, Kurata M, et al. Hematopoietic Cell Transplantation for Severe Combined Immunodeficiency Patients: a Japanese Retrospective Study. J Clin Immunol. 2021;41(8):1865–77. [PubMed: 34448087]
36. Tsilifis C, Lum SH, Nademi Z, et al. TCRalphabeta-Depleted Haploidentical Grafts Are a Safe Alternative to HLA-Matched Unrelated Donor Stem Cell Transplants for Infants with Severe Combined Immunodeficiency. J Clin Immunol. 2022;42(4):851–8. [PubMed: 35305204] TCRαβ depleted haploidentical transplants can achieve outcomes similar to HLA matched HSCT
37. Elfeky R, Shah RM, Unni MNM, et al. New graft manipulation strategies improve the outcome of mismatched stem cell transplantation in children with primary immunodeficiencies. J Allergy Clin Immunol. 2019;144(1):280–93. [PubMed: 30731121]
38. Miggelbrink AM, Logan BR, Buckley RH, et al. B-cell differentiation and IL-21 response in IL2RG/JAK3 SCID patients after hematopoietic stem cell transplantation. Blood. 2018;131(26):2967–77. [PubMed: 29728406]
39. Delmonte OM, Castagnoli R, Yu J, et al. Poor T-cell receptor beta repertoire diversity early posttransplant for severe combined immunodeficiency predicts failure of immune reconstitution. J Allergy Clin Immunol. 2022;149(3):1113–9. [PubMed: 34384841] **Identifies a clinical assay that can be used to predict poor immune reconstitution following transplant
40. Stephan V, Wahn V, Le Deist F, et al. Atypical X-linked severe combined immunodeficiency due to possible spontaneous reversion of the genetic defect in T cells. N Engl J Med. 1996;335(21):1563–7. [PubMed: 8900089]
41. Okuno Y, Hoshino A, Muramatsu H, et al. Late-Onset Combined Immunodeficiency with a Novel IL2RG Mutation and Probable Revertant Somatic Mosaicism. J Clin Immunol. 2015;35(7):610–4. [PubMed: 26407811]

42. Blanco E, Izotova N, Booth C, et al. Immune Reconstitution After Gene Therapy Approaches in Patients With X-Linked Severe Combined Immunodeficiency Disease. Front Immunol. 2020;11:608653. [PubMed: 33329605] *Reviews developments and challenges in gene therapy for X-SCID over the last two decades
43. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science. 2000;288(5466):669–72. [PubMed: 10784449]
44. Hacein-Bey-Abina S, Le Deist F, Carlier F, et al. Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med. 2002;346(16):1185–93. [PubMed: 11961146]
45. Gaspar HB, Cooray S, Gilmour KC, et al. Long-term persistence of a polyclonal T cell repertoire after gene therapy for X-linked severe combined immunodeficiency. Sci Transl Med. 2011;3(97):97ra79.
46. Hacein-Bey-Abina S, Hauer J, Lim A, et al. Efficacy of gene therapy for X-linked severe combined immunodeficiency. N Engl J Med. 2010;363(4):355–64. [PubMed: 20660403]
47. Hacein-Bey-Abina S, von Kalle C, Schmidt M, et al. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. N Engl J Med. 2003;348(3):255–6. [PubMed: 12529469]
48. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science. 2003;302(5644):415–9. [PubMed: 14564000]
49. Hacein-Bey-Abina S, Garrigue A, Wang GP, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest. 2008;118(9):3132–42. [PubMed: 18688285]
50. Howe SJ, Mansour MR, Schwarzwaelder K, et al. Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. J Clin Invest. 2008;118(9):3143–50. [PubMed: 18688286]
51. Hacein-Bey-Abina S, Pai SY, Gaspar HB, et al. A modified gamma-retrovirus vector for X-linked severe combined immunodeficiency. N Engl J Med. 2014;371(15):1407–17. [PubMed: 25295500]
52. De Ravin SS, Wu X, Moir S, et al. Lentiviral hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. Sci Transl Med. 2016;8(335):335ra57.
53. Mamcarz E, Zhou S, Lockey T, et al. Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1. N Engl J Med. 2019;380(16):1525–34. [PubMed: 30995372]
54. Touzot F, Moshous D, Creidy R, et al. Faster T-cell development following gene therapy compared with haploidentical HSCT in the treatment of SCID-X1. Blood. 2015;125(23):3563–9. [PubMed: 25869287]
55. Hsieh EW, Hernandez JD. Clean up by aisle 2: roles for IL-2 receptors in host defense and tolerance. Curr Opin Immunol. 2021;72:298–308. [PubMed: 34479098] *A review highlighting lessons learned on IL-2R biology from human IEIs
56. Stepensky P, Keller B, Shamriz O, et al. T(+) NK(+) IL-2 Receptor gamma Chain Mutation: a Challenging Diagnosis of Atypical Severe Combined Immunodeficiency. J Clin Immunol. 2018;38(4):527–36. [PubMed: 29948574]
57. Ibusuki A, Nishikawa T, Hiraki T, et al. Prominent dermal Langerhans cells in an Omenn syndrome patient with a novel mutation in the IL2RG gene. J Dermatol. 2019;46(11):1019–23. [PubMed: 31456262]
58. Lim CK, Abolhassani H, Appelberg SK, et al. IL2RG hypomorphic mutation: identification of a novel pathogenic mutation in exon 8 and a review of the literature. Allergy Asthma Clin Immunol. 2019;15:2. [PubMed: 30622570]
59. Fernandez IZ, Baxter RM, Garcia-Perez JE, et al. A novel human IL2RB mutation results in T and NK cell-driven immune dysregulation. J Exp Med. 2019;216(6):1255–67. [PubMed: 31040184]
60. Zhang Z, Gothe F, Pennamen P, et al. Human interleukin-2 receptor beta mutations associated with defects in immunity and peripheral tolerance. J Exp Med. 2019;216(6):1311–27. [PubMed: 31040185]

61. Fuchs S, Rensing-Ehl A, Erlacher M, et al. Patients with T(+)/low NK(+) IL-2 receptor gamma chain deficiency have differentially-impaired cytokine signaling resulting in severe combined immunodeficiency. Eur J Immunol. 2014;44(10):3129–40. [PubMed: 25042067]
62. Vignoli M, Ciullini Mannurita S, Fioravanti A, et al. CD25 deficiency: A new conformational mutation prevents the receptor expression on cell surface. Clin Immunol. 2019;201:15–9. [PubMed: 30742970]
63. Aoki CA, Roifman CM, Lian ZX, et al. IL-2 receptor alpha deficiency and features of primary biliary cirrhosis. J Autoimmun. 2006;27(1):50–3. [PubMed: 16904870]
64. Bezrodnik L, Caldirola MS, Seminario AG, et al. Follicular bronchiolitis as phenotype associated with CD25 deficiency. Clin Exp Immunol. 2014;175(2):227–34. [PubMed: 24116927]
65. Al Sukaiti N, Al Sinani A, Al Ismaily S, et al. Pulmonary hemorrhage in a case of CD25 deficiency. LymphoSign Journal. 2014;01(01):39–43.
66. Caudy AA, Reddy ST, Chatila T, et al. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. J Allergy Clin Immunol. 2007;119(2):482–7. [PubMed: 17196245]
67. Sharfe N, Dadi HK, Shahar M, et al. Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. Proc Natl Acad Sci U S A. 1997;94(7):3168–71. [PubMed: 9096364]
68. Gilmour KC, Fujii H, Cranston T, et al. Defective expression of the interleukin-2/interleukin-15 receptor beta subunit leads to a natural killer cell-deficient form of severe combined immunodeficiency. Blood. 2001;98(3):877–9. [PubMed: 11468191]
69. Arcas-Garcia A, Garcia-Prat M, Magallon-Lorenz M, et al. The IL-2RG R328X nonsense mutation allows partial STAT-5 phosphorylation and defines a critical region involved in the leaky-SCID phenotype. Clin Exp Immunol. 2020;200(1):61–72. [PubMed: 31799703]
70. Elina AT, Juha G, Tiina Ö, et al. Novel Hemizygous IL2RG p.(Pro58Ser) Mutation Impairs IL-2 Receptor Complex Expression on Lymphocytes Causing X-Linked Combined Immunodeficiency. Journal of Clinical Immunology. 2020;40:503–14. [PubMed: 32072341]
71. Focosi D, Bestagno M, Burrone O, et al. CD57+ T lymphocytes and functional immune deficiency. J Leukoc Biol. 2010;87(1):107–16. [PubMed: 19880576]
72. Caldirola MS, Rodriguez Broggi MG, Gaillard MI, et al. Primary Immunodeficiencies Unravel the Role of IL-2/CD25/STAT5b in Human Natural Killer Cell Maturation. Front Immunol. 2018;9:1429. [PubMed: 29988287]
73. Laroni A, Uccelli A. CD56bright Natural Killer Cells: A Possible Biomarker of Different Treatments in Multiple Sclerosis. J Clin Med. 2020;9(5).
74. Stallone G, Infante B, Di Lorenzo A, et al. mTOR inhibitors effects on regulatory T cells and on dendritic cells. J Transl Med. 2016;14(1):152. [PubMed: 27245075]
75. Egg D, Rump IC, Mitsuiki N, et al. Therapeutic options for CTLA-4 insufficiency. J Allergy Clin Immunol. 2022;149(2):736–46. [PubMed: 34111452]
76. Klemann C, Esquivel M, Magerus-Chatinet A, et al. Evolution of disease activity and biomarkers on and off rapamycin in 28 patients with autoimmune lymphoproliferative syndrome. Haematologica. 2017;102(2):e52–e6. [PubMed: 27789675]
77. Forbes LR, Vogel TP, Cooper MA, et al. Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. J Allergy Clin Immunol. 2018;142(5):1665–9. [PubMed: 30092289]
78. Deya-Martinez A, Riviere JG, Roxo-Junior P, et al. Impact of JAK inhibitors in pediatric patients with STAT1 gain of function (GOF) mutations-10 children and review of the literature. J Clin Immunol 2022; 42:1071–1082. [PubMed: 35486339]
79. Hadjadj J, Fremond ML, Neven B. Emerging Place of JAK Inhibitors in the Treatment of Inborn Errors of Immunity. Front Immunol. 2021;12:717388. [PubMed: 34603291] *Summarizes experience to date with JAKinibs for IEIs and highlights unmet needs
80. Chan AY, Torgerson TR. Primary immune regulatory disorders: a growing universe of immune dysregulation. Curr Opin Allergy Clin Immunol. 2020;20(6):582–90. [PubMed: 32941318] *Describes the rapidly growing genetic causes of primary immune regulatory disorders

81. Chan AY, Leiding JW, Liu X, et al. Hematopoietic Cell Transplantation in Patients With Primary Immune Regulatory Disorders (PIRD): A Primary Immune Deficiency Treatment Consortium (PIDTC) Survey. Front Immunol. 2020;11:239. [PubMed: 32153572] *A survey of HSCT experience in multiple primary immune regulatory disorders demonstrated resolution of disease in more than half of the patients transplanted

82. Joosse ME, Charbit-Henrion F, Boisgard R, et al. Duplication of the IL2RA locus causes excessive IL-2 signaling and may predispose to very early onset colitis. Mucosal Immunol. 2021;14(5):1172–82. [PubMed: 34226674]

KEY POINTS

- IL-2R subunit deficiencies may present with infectious and/or inflammatory complications
- Management of infectious and inflammatory/autoimmune complications can determine outcomes for definitive treatment with HSCT or gene therapy
- IL-2Rα deficiency and hypomorphic IL-2Rβ and IL-2Rγ defects present with common immunological clinical laboratory findings including i) increased serum IL-2, ii) increased memory T cells, and iii) increased $CD56^{bright}$ NK cells

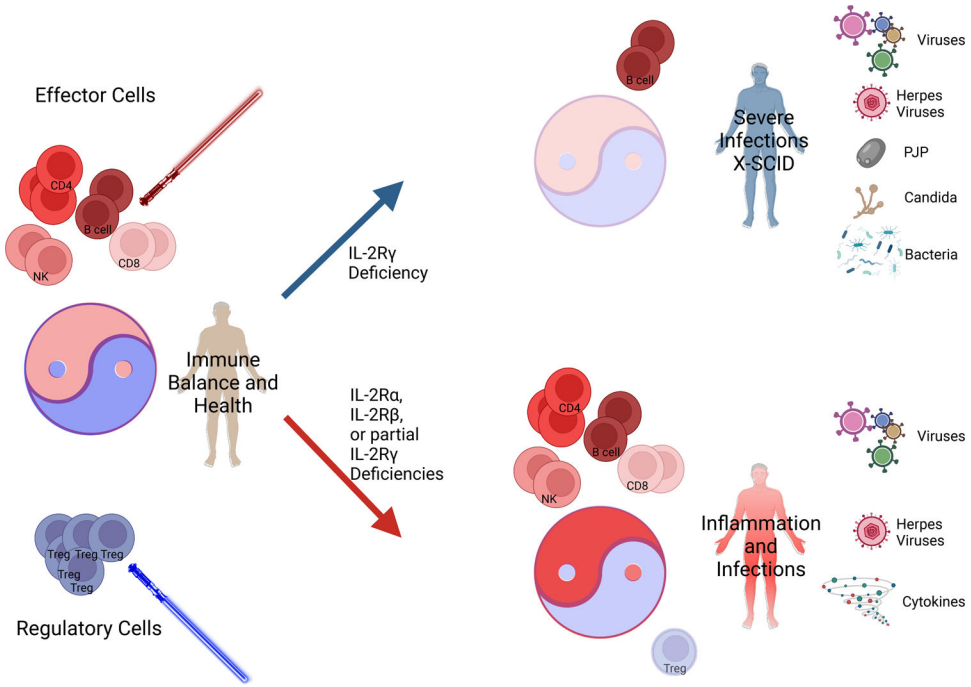

Figure 1.

Illustration of the role of IL-2/2R axis in the maintenance of immune tolerance and host defense.

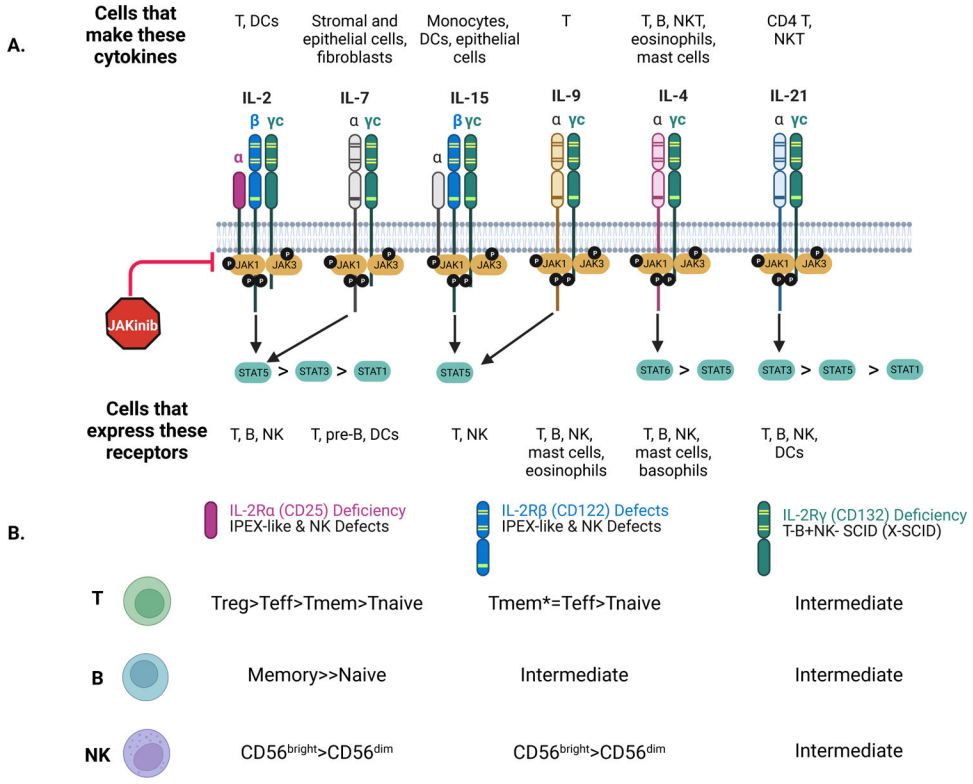

Figure 2. IL-2R subunits are expressed differentially across multiple immune cell subsets.

The IL-2R chains are shared by multiple cytokine receptors. All the receptors signal through JAK1 and JAK3 to activate downstream STATs, including STAT5. Unlike the other cytokines shown, IL-15 primarily exists bound to the high affinity IL-15Rα. When IL-15/IL-15Rα arrive to the cell surface, they can stimulate IL-2Rβγ_c via trans-presentation. **A**. IL-2R subunits are shown, with the cell types that secrete such cytokines, and the cell types that express the specific cytokine receptors. **B**. IL-2R subunits expression on different lymphocyte subsets are shown. “Intermediate” denotes expression levels in between none/low (i.e. CD25 on naïve T cells) and highly expressed (i.e. CD25 on Tregs).

Table 1.

Summary of immunological laboratory findings for IL-2R subunit defects that can be assessed from reference clinical and commercial laboratories.

Immunological Laboratory Finding	IL-2Rα (CD25)	IL-2Rβ (CD122)	IL-2Rγ (CD132)	Atypical IL-2Rγ (CD132)
Abnormal newborn screen (low TRECs)	−	−	+	+/−
Skewed memory T cell phenotype (CD45RO+)[1–5]	+	+	NA	+
Activated T cell phenotype ($PD1^{hi}$, $CD95^{hi}$)[3]	+	+	NA	+
Decreased regulatory T cells[1–5]	+/−	+	NA	+/−
Increased serum IL-2[2–4]	+	+	−	+/−
Increased total IgG/A	+	+	−	+/−
Decreased T cell proliferation to anti-CD3/28[3,5]	+	−	NA	−
Increased $CD56^{bright}$ NK cells[1]	+	+	NA	−
Normal NK cell killing/cytotoxic function[3,6]	+	+	NA	+

NA: Not Available, given lack of (or very low) T and NK cells in X-linked SCID due to IL-2Rγ deficiency

1. Mayo Clinic Laboratories
2. Associated Regional and University Pathologists, Inc. (ARUP) Laboratories
3. Cincinnati Children's Diagnostic Immunology Lab
4. National Jewish Health (NJH) Immune Diagnostic Lab
5. Medical College Wisconsin (MCW) Clinical Immune Diagnostic Lab
6. Quest Diagnostics